Remarks

Claims 1-8 are pending. Claims 1-8 stand rejected. Claim 1 is amended. Support for the amendment can be found, *inter alia*, at paragraph [0047] of the specification. Applicants submit that no new matter is added by the amendment herein.

Applicants have reviewed the Office Action, including the Examiner's remarks and the references cited therein. Applicants submit that the following remarks are fully responsive to the Office Action, and that all pending claims are patentable over the cited references.

Request for Reconsideration of Finality

This Office Action is a second action containing a new ground of rejection. A second action containing new grounds of rejection cannot be made final unless the new grounds of rejection are "necessitated by applicant's amendment of the claims" or "based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p)." MPEP § 706.07(a).

Contrary to the Examiner's assertion, the new grounds of rejection introduced in the second final action were not "necessitated by applicant's amendment of the claims." Rather, the rejection could have been made in the first Office Action, affording the Applicants an appropriate opportunity to reply. Indeed, the Henkart, Haake, Squier, Maki, and Ramsby references cited in the second action allegedly disclose the following "limitations": (1) calpastatin's role as a calpain inhibitor (Henkart, Squier, Maki) (2) use of calpastatin derivatives (Henkart, Maki) (3) use of other calpain inhibitors (Squier) (4)

p53's role in apoptosis (Haake) (5) differential detergent fractionation of p53 (Ramsby) (6) use of electrophoresis (Henkart, Squier, Ramsby).

All of these alleged "limitations" were present in the original, unamended claims. More specifically, claim 2 has always disclosed that the inhibitor is a calpastatin, meaning that the Henkart, Squier, and Maki references could have been cited in the initial Office Action. Moreover, independent claim 1 has always disclosed "providing a cell extract containing one or more p53 proteins," meaning that Haake and Ramsby could have been cited in the initial Office Action.

Applicants respectfully submit that the new grounds of rejection were not "necessitated by applicant's amendment of the claims." For at least the foregoing reasons, Applicants request reconsideration and withdrawal of the finality of the Office Action.

Rejections Under 35 U.S.C. § 103

Claims 1-8 stand rejected under 35 U.S.C. § 103, as allegedly being unpatentable over Henkart (US 5,607,831), in view of Squier et al. (Journal of Cellular Physiology, May 1994; 159(2): 229-237), further in view of Maki et al. (The Journal of Biological Chemistry, Nov. 15, 1989; 264(32): 18866-18869), further in view of Ramsby et al. (Electrophoresis, Feb. 1994; 15(2): 265-67, and further in view of Haake et al. (J. Invest. Dermatol, 1993; 101: 107-112). Applicants respectfully disagree for at least the following four reasons.

First, although the prior art references need not teach or suggest each and every limitation of a claim for that claim to be obvious, Applicants contend that the differences

between the rejected claims and the references cited are sufficiently great so as to fall short of any appropriate standard for a *prima facie* case here. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57527-28 (Oct. 10, 2007) ("[T]he focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and *on what such a person would have reasonably expected to have been able to do in view of that knowledge*.") (emphasis added). Moreover, "[i]f an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious." MPEP § 2143.03 (quoting *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988)). Applicants contend that the cited references fail to teach or suggest at least step 2 of claim 1, *i.e.*, "administering a peptide or protein inhibitor of calpain protease activity."

Prior to amendment, independent claim 1 had three specific steps: (1) providing a cell extract containing one or more p53 proteins and one or more proteases (2) administering a peptide or protein inhibitor of calpain protease activity, and (3) measuring p53 and p53 protein fragments. The skilled artisan would understand step 2 to mean that the peptide or protein inhibitor is administered to the cell extract containing one or more p53 proteins and one or more proteases, given that an enzyme inhibitor "interact[s] in some way with [an] enzyme to prevent it from working in the normal manner." Charles E. Ophardt, *Enzyme Inhibitors*, Virtual Chembook (2003) (attached as Exhibit A).

In other words, to administer a peptide or protein inhibitor of calpain protease activity in isolation is nonsensical; rather, the only sensible reading, and the reading that would be understood by one of ordinary skill in the art, is that the peptide or protein inhibitor is administered to the extract containing p53 and a protease - the enzyme with which the inhibitor specifically interacts. Moreover, the specification fully supports this reading, as Example 1.2 of paragraph 47 notes that:

> [A]ddition of m-calpain induced degradation of the p53 proteins. In this example, *in addition to m-calpain*, various compounds were introduced into the medium in order to test their capacity to inhibit the activity of calpain. The results obtained show that the addition of a calcium chelator (EGTA) as well as of a peptide which is a specific inhibitor of the calpains (derivative of a physiological inhibitor, *calpastatin* . . .) are capable of inhibiting the degradation of the p53 proteins which is induced by the exogenous calpain.

Paragraph [0047] (emphasis added). Thus, the skilled artisan would understand the second step of claim 1 to refer to administration of a peptide or protein inhibitor of calpain protease activity to the cell extract containing one or more p53 proteins and one or more proteases. Nevertheless, Applicants have amended claim 1 to fully clarify that the peptide or protein inhibitor of calpain protease activity is administered to the cell extract.

Applicants respectfully contend that the second step of claim 1 is neither taught nor suggested by any of the cited references. The Examiner submits that Ramsby discloses use of EDTA as a calpain inhibitor. However, the Examiner fails to mention that the EDTA in the Ramsby reference is added to digitonin and Triton *buffers*, and not to a cell extract containing p53 and a protease. Ramsby, page 268, column 1, lines 47-50 ("The addition of EDTA to digitonin and Triton buffers enhances the rate and

selectivity of fractionation and prevents undesirable degradation of cellular proteins by calcium-activated proteases").

No other reference compensates for this deficiency. Squier only mentions calpastatin in the context of explaining potential reasons for changes in the activity of calpain, and does not disclose administration of calpastatin or any other calpain inhibitor of calpain protease activity to a cell extract containing p53 and a protease. *See* Squier, page 235, column 1, lines 4-6. Similarly, Maki discloses that an exon of the human calpastatin gene inhibits calpain, but does not even mention p53 or administration of calpastatin to an extract containing p53 in the context of its disclosure. *See* Maki, Abstract.

Moreover, Haake only discusses p53 in general terms, and does not mention calpain, calpastatin, or calpain inhibitors, or administration of them to a cell extract containing p53 and a protease. *See* Haake, page 109, column 2, lines 25-28; page 110, column 1, lines 23-48, column 2, lines 11-14; page 111, column 1, lines 48-51. Finally, Henkart does not mention p53 at all, and only discuses calpain inhibition by calpastatin. *See* Henkart, column 7, lines 40-50. Accordingly, Applicants submit that the claimed invention is substantially different from, and therefore nonobvious over, the asserted references.

Second, both the Squier and Henkart references teach away from a combination with the Haake and Rambsy references. The Federal Circuit has explicitly stressed that "[i]t is improper to combine references where the references teach away from their combination." *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983).

Squier discloses that "[p]reincubation with calpain inhibitors *prevented apoptosis* in thymocytes whether induced by dexamethasone or by low-level irradiation," and that "calpain is necessary for triggering apoptosis." Squier, column 2, lines 25-26. Moreover, Henkart discloses that "[c]alpain inhibitors are effective in preventing the progression to cell death and can restore cell function." Henkart, Abstract. These disclosures are completely at odds with the teachings of Applicants' invention.

Indeed, one of the objects of Applicants' invention is to *trigger apoptosis* in tumor cells by using calpain inhibitors to prevent calpain degradation of wild-type p53. *See* paragraphs [0007], [0011]. More specifically, Applicants have explicitly noted that:

> The present invention describes a new approach for the treatment of cancer, based on the use of compounds which modulate the activity of calpains on the p53 proteins, which make it possible either to activate the degradation of mutated p53 proteins, in order to block their tumorigenic effect and/or to enhance the presentation of immunogenic peptides, or to stabilize the wild-type p53 protein, in order to counterbalance the tumorigenic effect of the mutated proteins expressed in the tumors and/or <u>in order to induce the apoptosis of the tumour cells</u>.

Paragraph [0007] (emphasis added). There is no explanation for the contradictory statements from the primary document Henkart or the first secondary document Squier.

Thus, in view of the references cited by the Examiner, the skilled artisan would have absolutely no reason to combine p53 (mentioned briefly in Ramsby and Haake) with calpain and calpastatin (disclosed in Henkart and Squier) if the artisan's goal was to trigger apoptosis in tumor cells. If there is some other logical reason for combining these alleged teachings, it has not been expressed on the record. Instead, based on the teachings of Henkart, the skilled artisan would be led in an opposite direction, and would *avoid* using calpain inhibitors because of Henkart's explicit teaching that

"[c]alpain inhibitors are effective in preventing the progression to cell death and can restore cell function." Henkart, Abstract.

Moreover, in light of Squier's disclosure, the skilled artisan looking to trigger apoptosis in a tumor cell would likely conclude that preparation of a cell extract containing p53 would be unnecessary and superfluous. Instead, the skilled artisan would merely utilize calpain by itself, and would be led away from any use of calpain inhibitors or p53. Thus, because the Squier and Henkart references teach away from a combination with the Haake and Ramsby references, Applicants submit that any alleged obviousness has been rebutted.

Third, the Examiner's conclusion that the claims are obvious is at odds with both Supreme Court precedent and the MPEP. Indeed, the Supreme Court has explicitly stated that, for purposes of obviousness analysis, a fact finder "must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007); *see also* MPEP § 2141. Moreover, the MPEP specifically provides that "proceeding contrary to the accepted wisdom in the art is evidence of nonobviousness." MPEP § 2145 (citing *In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986)).

The Maki and Henkart references demonstrate the unpredictability of the claimed invention. Indeed, Maki specifically provides that "the physiological roles of calpain have not yet been clarified" - an unsurprising revelation in view of the fact that *Applicants* were the first group to discover that p53 proteins are substrates for calpain enzymatic activity. *See* Maki, page 18866, column 1, lines 5-6; *see also* Applicant's Reply and Amendment dated February 19, 2008, page 5 ("[A]pplicants explain and

show in the specification that they were the first to recognize that p53 proteins are direct substrates for calpain enzymatic activity . . . ."). Moreover, Henkart notes that "calpain inhibitors have been of therapeutic interest principally in two clinical situations," and proceeds to list stroke and muscular dystrophy as the relevant diseases. Henkart, column 1, lines 50-67. Thus, Applicants made their invention against a backdrop in which the precise physiological role of calpain was unclear. As such, Applicants respectfully submit that the unpredictability of the claimed invention serves as persuasive evidence of nonobviousness.

Fourth, the Examiner disregards the basic precept that obviousness is to be determined by looking at the claimed invention and the prior art references as a whole, and not by looking at the individual differences themselves. Indeed, the MPEP provides that "[i]n determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." MPEP § 2141.02 (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983)). Moreover, the MPEP provides that "[a]scertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole." MPEP § 2141.02.

The Ramsby and Haake references, when viewed as a whole, demonstrate the nonobviousness of the present invention. Indeed, Ramsby discloses a method for "differential detergent fractionation (DDF) which reproducibly partitions hepatocytic proteins into four distinct fractions and appears to preserve cytoskeletal interactions."

Ramsby, page 266, column 1, lines 48-52. The Examiner has provided no explanation as to why the skilled artisan would even consult this reference, or consider its teachings remotely relevant to detecting an inhibitor of p53 protein degradation. Rather, the Examiner merely highlights the presence of terms common to the reference and to the claims at issue, without providing a detailed rationale as to why the reference as a whole should even enter the equation. Applicants respectfully request that the Examiner explain why a person having ordinary skill in the art in the field would consult a source discussing differential detergent fractionation of hepatocytes.

Moreover, the Haake reference, when viewed as whole, does nothing more than provide a general overview of p53's role in apoptosis and the implications of a mutation in the p53 gene. The Haake reference does not come close to disclosing the inter-relationship between p53, calpain, or calpastatin, or the fact that p53 is a substrate of calpain. Again, the Examiner appears to be searching for individual terms common to the claims and references, and in the process disregards the MPEP's specific directive to consider the claims, references, and invention disclosure as a whole.

For these reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Having addressed each outstanding rejection and objection, Applicants request allowance of the application.

Applicants respectfully request entry of the amendments and timely notification of allowability. If there are any additional fees due with the filing of this document, or any attached document, including fees for the net addition of claims, applicants respectfully request that any and all fees be charged to Deposit Account No. 50-1129. If any

extension of time request or any petition is required for the entry of this paper or any of the accompanying papers, applicants hereby petition or request the extension necessary. The undersigned authorizes any fee payment from Deposit Account No. 50-1129. Furthermore, if additional extensions of time are required to enter this amendment beyond any provided for, applicants respectfully request an extension and the undersigned hereby authorizes that any fees be taken from Deposit Account No. 50-1129, referencing Attorney Docket No. 80375.0033.

Respectfully submitted,

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Date: October 30, 2008

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